

PROCESS FOR PREPARING LOSARTAN POTASSIUM WITH IMPROVED FLOWABILITY

RELATED APPLICATIONS

The present Application claims the benefit of the filing date of the following United States Provisional Patent Applications No. 60/419,450, filed October 17, 2002; No. 60/426,072, filed November 12, 2002; No. 60/426,461, filed November 14, 2002; No. 60/431,450, filed December 4, 2002 and No. 60/431,809, filed December 9, 2002.

FIELD OF THE INVENTION

[0001] The present invention relates to a new process for preparing, and to compositions containing, losartan potassium with improved flowability.

BACKGROUND OF THE INVENTION

[0002] Losartan potassium, also known as 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-buphenyl]-4-yl]-1H-imidazole-5-methanol monopotassium salt, is a competitive AT₁ angiotensin II receptor antagonist. Activation of AT₁ receptors in the outer membrane of vascular smooth muscle cells of the heart and arteries causes the tissues to constrict. AT₁ receptors are activated by an octa-peptide, angiotensin II. Angiotensin II helps to maintain constant blood pressure despite fluctuations in a person's state of hydration, sodium intake and other physiological variables. Angiotensin II also performs the regulatory tasks of inhibiting excretion of sodium by the kidneys, inhibiting norephedrin reuptake and stimulating aldosterone biosynthesis. By inhibiting angiotensin II binding to AT₁ receptors, losartan disrupts the vasoconstriction mediated by AT₁ receptors. Blocking vasoconstriction by angiotensin II has been found to be beneficial to patients with hypertension.

[0003] In 1995, losartan became the first nonpeptide AT₁ antagonist approved by the U.S. Food and Drug Administration for clinical use. In particular, losartan is approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Losartan may be administered orally as its monopotassium salt. Losartan potassium is available by prescription in tablet form as a sole active ingredient (Cozaar[®]: Merck) and as a co-active ingredient with hydrochlorothiazide (Hyzaar[®]: Merck).

[0004] The present invention relates to the solid state physical properties

of losartan potassium. These properties can be influenced by controlling the conditions under which losartan potassium is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

[0005] Losartan potassium can be prepared by a variety of methods. For instance, in U.S. Patent Nos. 5,128,355, 5,138,069 and 5,155,118, Example 316, Parts C and D respectively in all, trityl losartan (1-[(2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl)-methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole) was deprotected with a mixture of hydrochloric acid and methanol to form losartan free acid (2-butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)[1,1'-buphenyl]-4-yl)-1H-imidazole-5-methanol). Losartan potassium was formed by reacting losartan free acid with potassium hydroxide in a mixture of isopropyl alcohol and heptane.

[0006] In U.S. Patent No. 5,962,500, Example 5, and U.S. Patent Nos. 5,206,374 and 5,310,928, Example 21 in both, trityl losartan was deprotected with a mixture of aqueous sulfuric acid and tetrahydrofuran (THF), from which the salt was generated by extracting losartan from the mixture with an adsorbent, treating the adsorbent with dipotassium hydrogen phosphate and eluting losartan potassium from the adsorbent with 20% aqueous THF. The eluent was then concentrated and diluted with isopropyl alcohol, which yielded crystalline losartan potassium. Alternatively, the product was isolated by spray drying.

[0007] In U.S. Patents Nos. 5,130,439, 5,206,374 and 5,310,928, Example 8 in all, trityl losartan was deprotected with a mixture of aqueous hydrochloric acid and THF to form losartan free acid. Losartan potassium was formed by reacting losartan free acid with potassium hydroxide in a mixture of isopropyl alcohol, water and heptane.

[0008] Crystalline losartan potassium made from the processes described above is hygroscopic and has poor powder flow characteristics. Because of this poor

flowability, problems occur with handling and processing during milling and formulating. Solids that are fine, loose powders often have poor flow characteristics and are resistant to blending and dispersion in liquids because they clump and wet poorly. Dust associated with fine powders can develop a static charge and cling to equipment, making handling and feeding through volumetric equipment difficult.

[0009] In the past, powders with poor flow properties have been granulated to vary their particle size distribution in order to improve their characteristics. Other methods used to improve the flow properties of powders have been to treat the surface of the powdered material during manufacturing or to apply a lubricant to a powdered material that was to be subsequently processed.

[0010] The flowability of losartan potassium can be measured using the Hausner ratio, wherein a known weight of material is poured into a measuring cylinder, the volume recorded, and the poured density calculated. The cylinder is then tapped against a surface for a specified number of times, the new volume again recorded, and the tapped density calculated. The Hausner ratio is equal to tapped density divided by poured density. Henry H. Hausner, "Fiction Conditions in a Mass of Metal Powders," Int. J. Powder Metall. vol. 3, 1967, pp. 7-13. A ratio of <1.3 indicates a free flowing material while a ratio of >1.5 indicates a poor flowing material.

[0011] The flowability of dry crystals depends on many parameters such as crystal density, crystal size distribution, median crystal size, shape of the crystals, voidage fraction of the solids, degree of mixedness, inner voidage of crystals, residual moisture content, and concentration of adsorbed vapors and gases. A. Weissberger, II Organic Solvents, Physical Properties and Methods of Purification, 315 (4th Ed. 1986). The smaller the particles and the more the particles deviate from spheres, the stronger the friction and cohesion forces are, which results in reduced flowability. Further, the flowability of solid material may depend with time because parameters such as voidage fraction, interparticle forces and crystalline bridges, and adsorbates change with time and will influence such flowability.

[0012] To obtain more preferred crystals of losartan potassium, U.S. Patent No. 5,859,258 discloses the use of an antisolvent, to control the approach to

saturation and to control crystal growth, combined with massive seeding.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a method of increasing the flowability of losartan potassium powder initially having a Hausner ratio > 1.45 including the step of reslurrying such losartan potassium powder, especially such losartan potassium powder made by neutralization of the free acid in the presence of isopropanol, in a reslurry solvent selected from the hydrocarbons (especially the heptanes, cyclohexane, or toluene), the alkyl ethers, the alkyl esters, and mixtures of two or more of these. The method further includes the steps of isolating, drying, and, optionally, milling the losartan potassium. Losartan potassium so treated has Hausner ratio < 1.45 , especially ≤ 1.3 .

In another aspect, the present invention relates to a method of increasing the flowability of losartan potassium initially having a Hausner ratio > 1.45 including the steps of reslurrying such losartan potassium powder, especially such losartan potassium powder made by neutralization of the free acid in the presence of isopropanol, in a reslurry solvent selected from the heptanes, cyclohexane, and toluene. The method further includes the steps of isolating, drying, and milling the reslurried losartan potassium so treated. Losartan potassium so treated has Hausner ratio < 1.45 , especially ≤ 1.3 .

In another aspect, the present invention relates to losartan potassium having Hausner ratio < 1.45 , especially ≤ 1.3 obtained by a method including the step of reslurrying losartan potassium powder having Hausner ratio ≥ 1.45 , especially such losartan potassium powder made by neutralization of the free acid in the presence of isopropanol, in a reslurry solvent selected from the hydrocarbons (especially the heptanes, cyclohexane, or toluene), the alkyl ethers, the alkyl esters, and mixtures of two or more of these. The method further includes the steps of isolating, drying, and, optionally, milling the losartan potassium.

In still a further aspect, the present invention relates to pharmaceutical compositions including losartan potassium having Hausner ratio < 1.45 , especially \leq

1.3.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Losartan potassium that has been isolated (e.g. crystallized) by procedures using protic solvents in work-up or isolation has poor flowability, as indicated by a Hausner ratio of about 1.45-1.90. Powder of crystals of losartan potassium that has been subjected to the treatment method of the present invention has improved flowability as indicated by a Hausner ratio of about 1.3-1.45. A low Hausner ratio corresponds with crystals having high flowability. Measurement of Hausner ratio is well-known in the art and is described, for example, by Mersmann; Crystallization Technology Handbook (A. Mersmann, ed., 2nd ed., Marcel Dekker)

[0014] In one embodiment, the present invention provides a method for improving the flowability of crystals of losartan potassium having an initial Hausner ratio ≥ 1.45 that includes the step of reslurring crystals of losartan potassium in a reslurry solvent, preferably a hydrocarbon, alkyl ether, or alkyl ester reslurry solvent, whereby a slurry is obtained. In particular, the reslurring step involves contacting, with agitation, solid losartan potassium with a reslurry solvent in which losartan potassium is at most partially soluble.

[0015] The reslurring can be carried-out in any convenient equipment. The reslurring is preferably carried-out at the boiling point of the reslurry solvent. In this case, the refluxing action of the reslurry solvent can provide the agitation, but mechanical agitation can also be used.

[0016] The reslurry solvent is used in an amount of at least about 2 volumes or more, preferably more. "Volumes" is defined as 1 mL solvent per 1 gram of losartan potassium, e.g. "10 volumes" means 10 mL solvent per 1 gram of losartan potassium.

[0017] Reslurry solvents useful in the practice of the present invention include hydrocarbons, both aliphatic and aromatic. Examples of aliphatic hydrocarbons (i.e. alkanes) include the hexanes and the heptanes. Toluene is an example of an aromatic hydrocarbon. The aliphatic hydrocarbons can be essentially a single structural isomer (e.g. *n*-heptane), or they can comprise a mixture of structural isomers. The skilled artisan recognizes that the aliphatic hydrocarbons of commerce

can and frequently do comprise a mixture of normal and branched structures and such mixtures are useful in the practice of the present invention. Accordingly, as used herein, phrases such as “the heptanes” refers to a single isomer (e.g. *n*-heptane) as well as to mixtures of structural isomers (e.g. 2-methylhexane).

[0018] Cyclic alkanes such as cyclohexane and methylcyclohexane are also useful reslurry solvents that are hydrocarbons. Benzene, toluene, and the xylenes are aromatic hydrocarbons useful as reslurry solvents in the practice of the present invention.

[0019] The aliphatic ethers (dialkyl ethers) are also useful as reslurry solvents in the practice of the present invention. Aliphatic ethers have the structural formula $C_nH_{2n+1}-O-C_mH_{2m+1}$, wherein *n* and *m* are independently 2 to 6. Diethyl ether and methyl *t*-butyl ether are examples of aliphatic ethers useful in the practice of the present invention.

[0020] The alkyl esters of aliphatic carboxylic acids, especially acetic and propanoic acids, are also useful as reslurry solvents in the practice of the present invention. The alkyl esters have the structural formula $R_1-OC(O)R_2$, wherein R_1 and R_2 are, independently, normal or branched C1 to C5 alkyl. Ethyl acetate ($R_1 = C_2H_5$; $R_2 = CH_3$) is an example of an alkyl ester that is useful as a reslurry solvent in the practice of the present invention.

[0021] Preferred reslurry solvents include the hexanes, the heptanes, especially *n*-heptane, cyclohexane, toluene, diethyl ether, methyl *t*-butyl ether, ethyl acetate, and butyl acetate.

[0022] The reslurrying is carried-out for a time sufficient to effect the objectives of the present invention that can be determined by routine optimization. Reslurry times of about 3 to 10 hours are typically effective. At the end of the reslurry time, losartan potassium crystals are isolated from the slurry by known methods, for example filtration. The powder of isolated losartan potassium crystals is dried, preferably under vacuum, to obtain losartan potassium powder having improved flowability (Hausner ratio < 1.45).

[0023] The reslurry produces best results when the temperature of the reslurry is higher and the duration of the reslurry is longer. The resulting losartan

potassium can be isolated and dried by methods known in the art.

[0024] Examples of starting materials for the novel process include losartan potassium obtained by any of the methods described in the patents previously discussed, which employ protic solvents, *i.e.* U.S. Patents Nos. 5,128,355; 5,130,439; 5,138,069; 5,155,118; 5,206,374; 5,310,928; 5,608,075; 5,663,187; 5,663,186 and 5,962,500

[0025] The method of the present invention operates on losartan potassium of Hausner ratio ≥ 1.45 from any source. However, the benefits of the present invention are most prominent when losartan potassium made by a method that employs protic solvents is the starting material. For example, a preferred starting material is losartan potassium made from losartan free acid, wherein losartan free acid is contacted with a potassium base (*i.e.* a base having a potassium cation) in the presence of isopropyl alcohol. Potassium hydroxide is a preferred potassium base. Losartan potassium can be made via losartan free acid, preferably by contacting losartan free acid with a mixture of isopropyl alcohol and an antisolvent as discussed U.S. Patent No. 5,310,928 ("the '928 patent"), which is hereby incorporated by reference. Another preferred losartan free acid is made from trityl losartan, wherein trityl losartan is contacted with a mixture of water, acetone and sulfuric acid. Losartan free acid is also preferably made from trityl losartan, wherein trityl losartan is contacted with a mixture of water, THF, and sulfuric acid as discussed in the '928 patent.

[0026] Dried losartan potassium treated by the reslurry method of the present invention can be milled, for example using a cone mill, in order to delump the material and effect moderate size reduction. After such milling, the losartan potassium exhibits improved flowability properties.

[0027] In another embodiment, the present invention provides pharmaceutical compositions containing losartan potassium treated by the method of the present invention. Pharmaceutical compositions of the present invention contain losartan potassium having improved flowability, optionally in mixture with other active ingredients such as hydrochlorothiazide. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention can contain one or more

excipients, such as diluents, binders, disintegrants, glidants, and lubricants.

[0028] Diluents increase the bulk of a solid pharmaceutical composition and can make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates, potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

[0029] Solid pharmaceutical compositions that are compacted into a dosage form like a tablet can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate and starch.

[0030] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate and starch.

[0031] Glidants can be added to improve the flow properties of non-compacted solid composition and improve the accuracy of dosing. Excipients that can function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

[0032] When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and

dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

[0033] Selection of excipients and the amounts to use can be readily determined by the formulation scientist based upon experience and standard procedures in the field.

[0034] The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions.

[0035] Losartan potassium treated by the method of the present invention can be administered for treatment of hypertension by any means that delivers the active pharmaceutical ingredient(s) to the site of the body where competitive inhibition of an AT₁ receptor exerts a therapeutic effect on the patient. For example, administration can be oral, buccal, parenteral (including subcutaneous, intramuscular, and intravenous) rectal, inhalant and ophthalmic. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. Losartan potassium treated by the method of the present invention can be conveniently administered to a patient in oral unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts. Dosage forms include solid dosage forms like tablets, powders, capsules, sachets, troches and lozenges.

[0036] The active ingredient(s) and excipients can be formulated into compositions and dosage forms according to methods known in the art.

[0037] A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the

desired particle size. The granulate can then be tableted or other excipients can be added prior to tableting such as a glidant and/or lubricant.

[0038] A tableting composition can be prepared conventionally by dry blending. For instance, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can be compressed subsequently into a tablet.

[0039] As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[0040] A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

[0041] Yet more particularly, a tablet can, for example, be formulated by blending 100 mg spray dried lactose, 50 mg of losartan potassium treated by the method of the present invention, and 5 mg of magnesium stearate and directly compressing the composition in a tablet machine.

[0042] A capsule can, for example, be prepared by filling half of a gelatin capsule with the above tablet composition and capping it with the other half of the gelatin capsule.

[0043] Capsules, tablets and lozenges and other unit dosage forms preferably contain a dosage level of about 10 mg to about 100 mg, more preferably from about 25 mg to about 50 mg of losartan potassium treated by the method of the present invention.

[0044] The following examples are given for the purpose of illustrating the present invention and shall not be construed as limiting the scope or spirit of the invention.

EXAMPLES

Example 1

Preparation of Losartan Free Acid

[0045] Aqueous hydrochloric acid (3 N, 39.1 mL, 117.3 mmol (3 eq.)) was added to a suspension of trityl losartan (26.0 g, 39.1 mmol) in acetone (150 mL) at room temperature. The reaction mixture was stirred for about 5 hours. A solution of potassium hydroxide (85%, 11.0 g, 195.5 mmol, 5 eq.) in water (100 mL) was slowly added and acetone was evaporated under reduced pressure. A slightly yellow precipitate was filtered, washed with water (2x20 mL), and dried under reduced pressure (about 10 mm Hg) at about 50° C. Triphenyl methanol (10.1 g, 99% yield) was recovered in 94.6% purity as determined by HPLC.

[0046] Ethyl acetate (100 mL) was added to the aqueous filtrate and the two-phase mixture was vigorously stirred and acidified to pH 3.5-3.6 with slow addition of 3 N aqueous hydrochloric acid (about 25 mL). The resulting suspension was stirred for an additional 30 minutes and filtered. The wet cake was washed with ethyl acetate (50 mL) and an acetone/water (50:50, 50 mL) mixture and dried under reduced pressure for about 2 hours at about 50 °C. Losartan free acid (15.0 g, 91.0% yield) was obtained in 97.68% purity as determined by HPLC.

[0047] The phases of filtrate were separated and ethyl acetate phase (yellowish organic phase) was concentrated to 40 mL volume. The precipitate was formed and after about 20 hours of stirring at room temperature, the precipitate was collected by filtration and dried under reduce pressure to yield additional losartan free acid (0.9 g, 5.5% yield).

Example 2

Preparation of Losartan Potassium

[0048] A solution of potassium hydroxide (0.305 g, 4.62 mmol (1 eq.)) and isopropyl alcohol (15 mL) was slowly added to a suspension of losartan free acid (2.0 g, 4.73 mmol) in isopropyl alcohol (25 mL). The reaction mixture was stirred for about 2 hours at room temperature. The mixture was filtered, concentrated to about a 15 mL volume, heated to reflux and stirred for about 12 hours at room temperature. The precipitate was filtered, washed with isopropyl alcohol (5 mL), and dried under

reduced pressure for about 2 hours at about 50° C to give losartan potassium (1.85 g, 85% yield) as a white powder. Yield of losartan potassium starting from losartan trityl was about 78%. Purity was determined to be 99.74% by HPLC. Losartan potassium (1.0 g) was triturated with ethyl acetate (10 mL), having a purity of 99.775% by HPLC.

[0049] The overall yield of losartan potassium from trityl losartan was 78%.

Example 3

Preparation of Losartan Potassium with Improved Flowability

[0050] Dry losartan potassium (50 g) is reslurried in heptane (200 mL) at about 25° C for about 4 hours. The suspension is filtered and dried under vacuum at about 50-60° C for about 10 hours. The Hausner ratio is decreased from about 1.50-1.60 to about 1.30-1.40. Yield is about 98%.

Example 4

Preparation of Losartan Potassium with Improved Flowability

[0051] Dry losartan potassium (50 g) is reslurried in heptane (500 mL) at about 100° C for about 10 hours. The suspension is cooled to about 25° C, filtered and dried under vacuum at about 50-60° C for about 10 hours. The Hausner ratio is decreased from about 1.50-1.60 to about 1.30-1.35. Yield is about 98%.

Example 5

Preparation of Losartan Potassium with Improved Flowability

[0052] Dry losartan potassium (50 g) is reslurried in cyclohexane (200 mL) at about 80° C for about 4 hours. The suspension is filtered and dried under vacuum at about 50-60° C for about 10 hours. The Hausner ratio is decreased from about 1.50-1.60 to about 1.3-1.35. Yield is about 98%.

Example 6

Preparation of Losartan Potassium with Improved Flowability

[0053] Dry losartan potassium (50 g) is reslurried in toluene (200 mL) at about 25° C for about 4 hours. The suspension is filtered and dried under vacuum at about 50-60° C for about 10 hours. The Hausner ratio is decreased from about 1.50-1.60 to about 1.3-1.35. Yield is about 98%.